Yonago Acta Medica 2024;67(1):1–8 doi: 10.33160/yam.2024.02.001 *Review Article*

# Roles of Microglia in Neurodegenerative Diseases

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## ABSTRACT

In recent years, microglia have attracted attention owing to their roles in various neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Microglia, which are brain-resident macrophages, not only act as immune cells but also perform other functions in the body. Interestingly, they exert contrasting effects on different neurodegenerative diseases. In addition to the previously reported M1 (toxic) and M2 (protective) types, microglia now also include disease-associated microglia owing to a more elaborate classification. Understanding this detailed classification is necessary to elucidate the association between microglia and neurodegenerative diseases. In this review, we discuss the diverse roles of microglia in neurodegenerative diseases and highlight their potential as therapeutic targets.

**Key words** Alzheimer's disease; inflammation; microglia; Parkinson's disease; therapeutic target

Microglia, resident brain macrophages, are glial cells that play important roles in the immune functions of the central nervous system (CNS). They were originally described and named by Pío del Río Hortega.[1] Unlike neurons, astrocytes, and oligodendrocytes, which originate from the ectoderm, microglia originate from the mesoderm, and erythromyeloid progenitors (EMPs) are their precursor cells in the yolk sac.[2] They are different from hematopoietic stem cell (HSC)-derived macrophages. EMPs generated during early development migrate throughout the body; those that migrate to the liver, epidermis, lungs, and CNS differentiate into the Kupffer cells, Langerhans cells, alveolar macrophages, and microglia, respectively.[2] Subsequently, HSC-derived monocytes are replaced by differentiated macrophages in most tissues. Because they cannot penetrate the blood–brain barrier formed during development, replacement of HSC-derived macrophages is not observed in the brain.[3] Tracing of fetal and adult HSCs with the Flt3 marker has revealed that only 2% of brain microglia are HSC-derived in 1-year-old mice.[4] Microglia are distributed throughout the CNS, and are often identified by the expression of various cell-specific intracellular proteins, such as Iba1, CD11b, and C-X3-C motif chemokine receptor 1 (CX3CR1)[5–7] (Table 1). The expression of each marker differs depending on the microglial subtype and activation state. Hence, these markers should be properly used for neuroscience research.

Similar to macrophages, microglia play important roles as immune cells that phagocytose foreign substances and dead cells, and release chemokines and cytokines.[8] They quickly remove the unnecessary substances, such as foreign substances and dead cells, and their immune response induces the healing of the injured area.[8] Owing to these activities, some suggest that microglia play a key role in maintaining homeostasis in the CNS. However, microglia can also exacerbate the damage in progressive neurodegenerative diseases, neuronal damage, and chronic inflammatory responses.[9] Recently, activated microglia have been recognized as key players in the aggravation of various neurodegenerative diseases.[10, 11]

Microglia exhibit surprising behaviors in their morphology and functions in certain situations, drastically changing shape depending on their external environment.[12] Under normal conditions, microglia are of the resting type (ramified type) with elongated protrusions extending from their small cell body. They are activated due to nerve injuries, inflammation, or ischemia, leading to the enlargement of the cell body and shrinking of the protrusions, thus forming an amoeboid shape resembling that of macrophages.[12] Based on their function, microglia are of two types: M1 (neurotoxic)

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Received 2024 January 11
Accepted 2024 January 24
Online published 2024 February 20

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ATPRs, ATP receptors; CCL, C–C motif chemokine ligand; CNS, central nervous system; CX3CR1, C-X3-C motif chemokine receptor 1; DAM, Disease-associated microglia; DAMP, damage-associated molecular patterns; EMP, erythromyeloid progenitor; FAD, familial Alzheimer's disease; HMGB1, High Mobility Group Box 1; HSC, hematopoietic stem cell; IL, interleukin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; PD, Parkinson's disease; PET, positron emission tomography; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF, tumor necrosis factor; TREM, triggering receptor expressed on myeloid cells

**Table 1. Major markers for microglia**

| Marker molecule | Function | Distribution | Further information |
|---|---|---|---|
| Iba 1 | Ca binding protein | Membrane ruffle | |
| TREM2 | Receptor for phagocytosis? | Membrane | |
| CX3CR1 | Fractalkine receptor | Membrane | |
| F4/80 | Adhesion G protein coupled receptor E1 | Membrane | |
| CD11b | Immune function ? | Membrane | CD11b/CD40 ↑:MG, CD11b/CD40 ↓: macrophage |
| CD68 | Protection of lysosomal membrane | Lysosome | |
| TREM119 | Unknown | Membrane | MG specific |

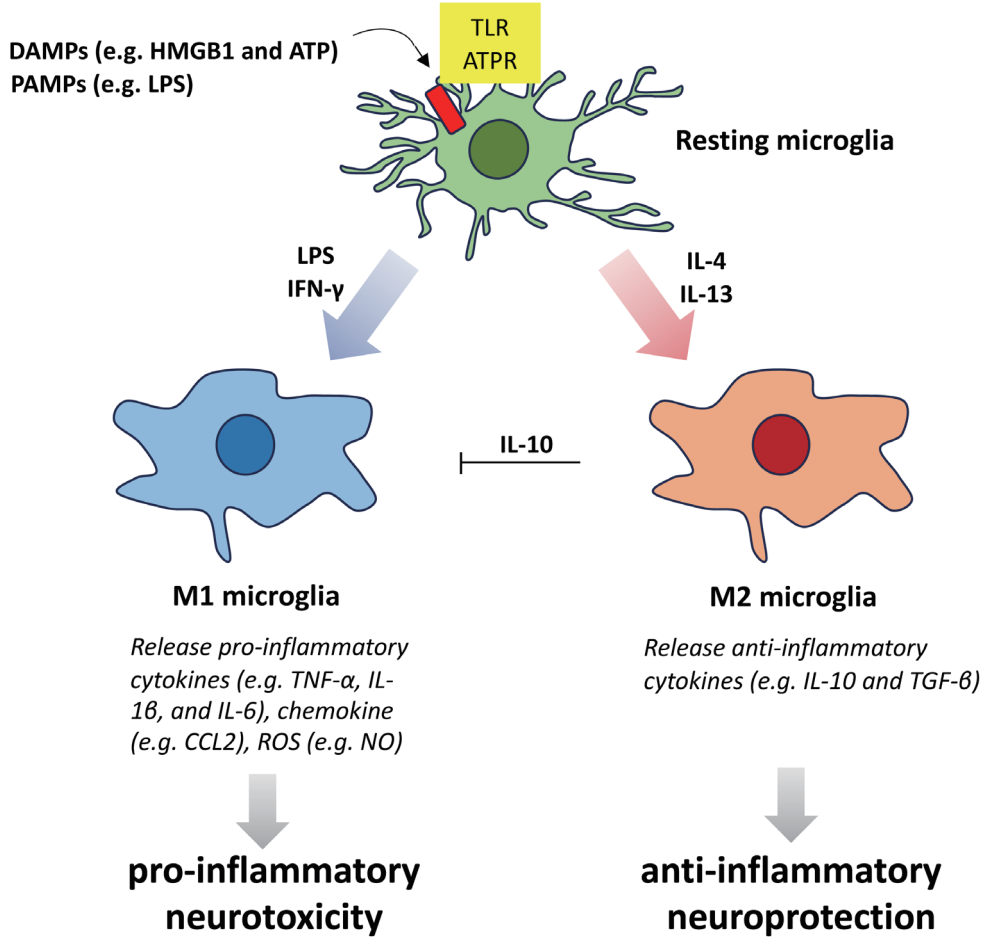


**Fig 1.** M1 and M2 microglia. Damage-associated molecular patterns (DAMPs) act on various inflammation-related receptors, including the toll-like receptors (TLRs) and ATP receptors (ATPRs), in resting microglia to induce the formation of M1 or M2 microglia. M1 microglia induce a proinflammatory state and tissue damage by releasing tumor necrosis factor (TNF)-α, interleukin (IL)-1b, IL-6, C–C motif chemokine ligand (CCL)-2, and reactive oxygen species (ROS) such as nitric oxide (NO). In contrast, M2 microglia exert tissue-protective effects by releasing anti-inflammatory cytokines such as IL-10, and transforming growth factor (TGF)-β. IL-10 inhibits the activation of M1 microglia. M1 microglia are pro-injury, whereas M2 microglia are anti-injury. HMGB1, High Mobility Group Box 1.

and M2 (neuroprotective) microglia (Fig. 1).[11, 13, 14] M1 microglia are predominantly observed in the brain of patients with neurodegenerative diseases.[13] M1 microglia recognize interferon-γ, tumor necrosis factor (TNF)-α, and damage-associated molecular patterns (DAMPs) and release inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and TNF-α, and reactive oxygen species, such as nitric oxide.[11, 15, 16] In contrast, M2 microglia

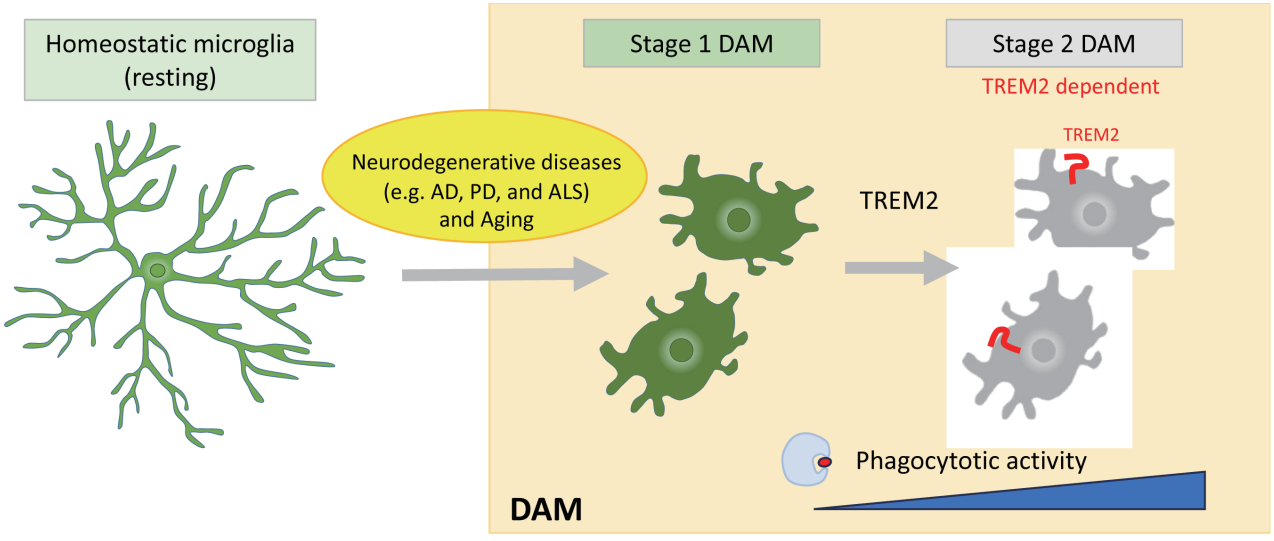


**Fig 2.** Disease-associated microglia (DAM) and the two-step model of DAM induction. Several signaling pathways induced during the pathogenesis of neurodegenerative diseases and/or aging promote the transition of microglia from homeostatic to stage 1 DAM. The triggering receptor expressed on myeloid cells 2 (TREM2) signaling further induces the transition to stage 2 DAM. This figure is cited and modified from reference [26].

recognize IL-4 and transforming growth factor (TGF)-β and release anti-inflammatory cytokines, such as IL-10 and TGF-β, and neurotrophic factors, such as the brain-derived neurotrophic factor.[11, 17–19] Many attempts have been made to explore other subtypes of microglia.[20] Recently, single-cell RNA-seq revealed that mouse microglia can be divided into at least nine clusters.[20] Additionally, microglia can play various roles, such as extend their projections into neuronal synapses, monitor the state of neurons via direct contact, and participate in synaptic pruning during CNS development.[21, 22]

Microglia can either promote or suppress the progression of various CNS diseases.[11–13] Even in the same disease, the activation status of microglia can be diverse and complex depending on the degree of disease progression and affected brain region. Previous pathological observations suggest the existence of different microglial subtypes, each of which performs various functions.[11–13] Advances in omics techniques, such as transcriptomics and proteomics, have facilitated the analysis of cell classification systems and functional characteristics at the genetic level with high sensitivity. In particular, single-cell analysis technologies, such as single-cell RNA-seq, which have made rapid progress recently, are useful for cell diversity analysis.[20, 23, 24]

Masuda et al. investigated the detailed classification of microglia using different cutting-edge technologies, such as single-cell RNA sequencing.[25] They revealed that different types of microglia exhibit distinct gene expression profiles during development. Using a mouse model of CNS disease, microglia were isolated from pathological lesions, and their genetic profiles were analyzed. The results revealed that microglia isolated from pathological lesions in the brain exhibit a completely different genetic profile than the normal microglia, showing different gene expression patterns in different animal models.[25] Moreover, microglia in a demyelination model were classified into two types based on their gene expression patterns, suggesting that each type performs different functions.[25] Masuda et al. also reported that microglia shift to an activated state under pathological conditions, showing genetic changes in a context-dependent manner to appropriately respond to each situation.[25]

## DISEASE-ASSOCIATED MICROGLIA (DAM)

Microglia exhibit a common activation state (DAM) in aging and neurodegenerative diseases, and their involvement in the pathology of various neurodegenerative diseases has attracted attention in recent years.[26, 27] DAM are primarily observed in the disease-affected CNS regions, but not in the healthy regions, suggesting their role in the pathogenesis of neurodegenerative diseases.[27] Keren-Shaul et al. identified DAM via single-cell RNA-seq analysis in Alzheimer's disease (AD) model mice.[26] They classified DAM into two stages: stages 1 and 2 DAM. The transition from homeostatic to stage 1 DAM requires various stimuli, such as aging, amyloid plaques in AD, and neuronal death due to amyotrophic lateral sclerosis (ALS). Moreover, the

triggering receptor expressed on myeloid cells (TREM)-2 stimulation is important for the transition from stage 1 to stage 2 DAM (Fig. 2). Notably, stage 2 DAM are the main disease-associated phagocytes in AD.[26]

DAM are molecularly characterized as immune cells expressing typical microglial markers, such as Iba1, Cst3, and Hexb, and downregulating the expression levels of homeostatic microglial genes, including P2ry12, P2ry13, Cx3cr1, CD33, and Trem119.[18] In contrast, DAM upregulates the levels of genes involved in lysosomal, phagocytic, and lipid metabolism pathways, including several known AD risk factors, such as ApoE, Ctsd, Lpl, Tyrobp, and TREM2.[27]

## MICROGLIA IN NEURODEGENERATIVE DISEASE

### Microglia in AD

AD, the most common neurodegenerative disease, is characterized by cognitive decline in old age. The β-amyloid (Aβ) hypothesis has been proposed as a mechanism for the onset of AD; microglia around senile plaques, which are Aβ aggregates, are activated in the brain of patients with AD.[28, 29] Similarly, clusters of activated microglia are observed around Aβ aggregates in the brain of AD model mice (Fig. 3).

Similar to other macrophages, microglia possess phagocytic abilities. Activated microglia phagocytose and degrade Aβ aggregates, thereby suppressing AD. Therefore, disruption in Aβ clearance by microglia may be a potential cause for AD pathogenesis.[30]

Although various cytokines, such as TNF-α, IL-1β, and IL-6, glutamate, and reactive oxygen species released by microglia mainly promote the progression of AD, microglia are suggested to play antagonistic roles in AD progression depending on the situation.[31]

Mechanisms involved in amyloid uptake by microglia include phagocytosis, pinocytosis, and receptor-dependent endocytosis.[32] Phagocytosis facilitates the uptake of polymerized insoluble amyloids, whereas pinocytosis facilitates the uptake of less polymerized amyloids. Pattern recognition receptors, such as toll-like receptors (TLRs) and scavenger receptors, are involved in receptor-dependent endocytosis.[33] CD14 is important as a co-receptor for TLRs.[34]

The R47H mutation in TREM2, which is expressed in microglia, is a risk factor for AD,[35, 36] and the association between microglia and AD has attracted attention recently. TREM2 abnormalities cause the early onset of dementia in patients with the Nasu-Hakola disease, suggesting that abnormalities in microglial function are associated with cognitive function.[37] TREM2 may be a receptor for Aβ as its deletion increases the Aβ aggregates in 5×FAD model mice with familial AD risk mutations.[38] Moreover, the AD-associated R47H mutation in TREM2 may alter its phagocytotic function.[39] TREM2 recognizes lipids associated with Aβ accumulation and cell damage and plays an important role in detecting CNS and associated response abnormalities.[40] Microglial TREM2 regulates the spread of tau proteins, which are components of neurofibrillary tangles.[41]

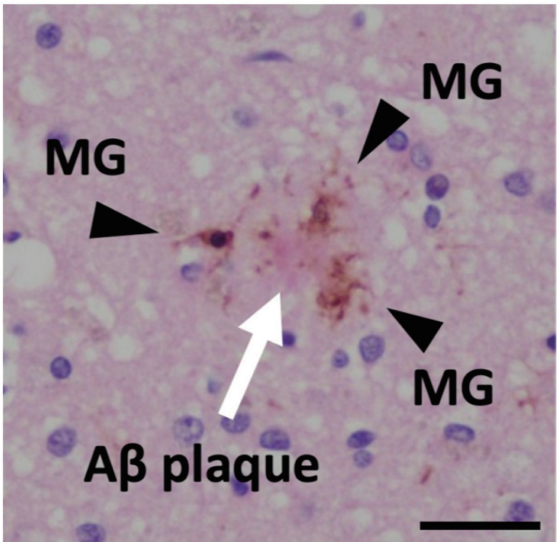


**Fig 3.** Accumulation of microglia around the amyloid plaque. Iba-1-positive macrophages (black arrowheads) are observed around a senile plaque (white arrow). Scale bar = 100 μm. This picture was kindly provided by Dr. Tadashi Adachi (Tottori University). MG, microglia.

### Microglia in Parkinson's disease (PD)

PD is a neuropathological disorder involving the degeneration of dopaminergic neurons in the substantia nigra, with subsequent loss of their terminals in the striatum.[42] Microglial activation is observed in the brain of patients with PD.[43, 44] In addition, levels of inflammatory cytokines (IL-1b, TNF-a, and IL-6) are elevated in the brain of patients with PD, indicating the importance of inflammation-based non-autonomous neuronal death in PD pathology.[45, 46] Microglia are activated by various proteins, such as leucine-rich repeat kinase 2, α-synuclein, parkin, and DJ-1, which cause familial PD.[47] Many studies are investigating the nature of this disease. Recent studies using [$^{11}$C-]-PK11195 positron emission tomography (PET) have shown that peripheral benzodiazepine receptors, which are abundantly expressed in glial cells, are associated with the onset of PD in patients with PD for approximately 10 years or dementia patients with Lewy bodies.[48, 49] They are prevalent in the basal ganglia and frontal lobe/temporal

lobe cortex. Another PET study reported an increase in the number of activated microglia in PD lesions.[48] Among animal models, the relationship between microglial activation and disease pathology has been extensively investigated in PD model mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Infiltration of Iba-1-positive and CD68-positive activated microglia is localized to the substantia nigra.[50] Furthermore, suppression of microglial function or inducible nitric oxide synthase/IL-1 expression via the administration of minocycline improves dopaminergic neuron death in MPTP-treated model mice.[51] These studies suggest the important roles of microglia in various pathological conditions.

### Microglia in ALS

ALS is an incurable neurological disease that causes the selective degeneration of motor neurons.[52] Activated microglia are observed in the motor nerve ablation area of the ventral horn of spinal cord. In a disease model based on the expression of mutant superoxide dismutase (SOD)-1, causative gene of hereditary ALS, mutant SOD1 expressed in microglia and astrocytes accelerated ALS pathology.[53] Another clinical study that analyzed microglial activation in sporadic ALS using PET reported that microglial activation in the cerebral cortex is correlated with the disease pathology.[54] Microglial xCT-mediated glutamate release outside the cells is involved in the pathology of ALS. Interestingly, ALS mice crossed with xCT knockout mice exhibit a long lifespan.[55]

## ASSOCIATION BET WEEN DEPRESSIVE SYMPTOMS AND MICROGLIA IN NEURODEGENERATIVE DISEASES

Many studies have shown that neuroinflammation is related to depressive symptoms,[56, 57] which are not only observed in depression but also in various neurodegenerative diseases, such as AD and PD. In recent years, the involvement of chronic neuroinflammation and microglial activation in depressive symptoms has attracted attention.[58] High serum IL-6 levels in childhood increase the risk of developing depression in adolescence in a concentration-dependent manner. A study demonstrated that psychosocial stress during childhood has long-term effects on the immune system via PET imaging,[58] which labels activated microglia, revealing the positive correlation between depressive symptoms and microglial activation in the prefrontal cortex, anterior cingulate cortex, and hippocampus in patients with depression.[58] These symptoms are also observed in patients with suicidal tendencies.[59] In a rat model of repeated social defeat stress, bone marrow hematopoiesis was promoted via the sympathetic nervous system, and immature monocytes migrated into the brain and activated microglia. Emotional response (anxiety-like behavior) caused by psychosocial stress causes peripherally derived monocytes and intracerebral microglia to mutually amplify neuroinflammation.[60] Similar microglial activation is observed in various neurodegenerative disease models, suggesting a common mechanism.

## ASSOCIATION BETWEEN BLOOD-BRAIN BARRIER DISRUPTION AND MICROGLIA IN NEURODEGENERATIVE DISEASES

The blood-brain barrier isolates the brain from the systemic circulatory system and maintains a constant environment by restricting the movement of substances into and out of the brain.[61] However, the functions of this barrier are impacted by systemic inflammation in neurodegenerative diseases, such as AD.[62] Haruwaka et al. investigated the process by which the blood–brain barrier breaks down due to systemic inflammation in mice and reported that the action of microglia on the blood–brain barrier becomes protective over time.[63] Microglia play an important role in the regulation of the blood–brain barrier functions. Inhibition of microglial activation ameliorates blood–brain barrier dysfunction. Abnormalities in blood–brain barrier function are observed in various neurodegenerative diseases, such as PD and AD,[64] suggesting the involvement of microglia-mediated blood–brain barrier functional abnormalities in various pathological conditions.

### Microglia as therapeutic targets for neurodegenerative diseases

Microglial activation is widely observed in various neurodegenerative diseases. However, microglial activation has little disease-specificity because it is a common mechanism in various diseases. Suppression of microglial activation may reduce the overall inflammation, inhibit the release of inflammatory cytokines and reactive oxygen species, and reduce glutamate release into the extracellular space by suppressing cystine/glutamate exchange transporters. Moreover, microglia can serve as targets for the treatment of various neurodegenerative diseases owing to their ability to phagocytose pathogenic proteins such as Aβ, and modulate the brain environment, including the blood–brain barrier. Because microglia change their characteristics depending on the surrounding environment, future studies should explore their roles and underlying mechanisms in the pathogenesis of different neurodegenerative diseases.

*Acknowledgements:* I appreciate to Dr Tadashi Adachi for giving a picture for immunohistochemistry. We would like to thank Editage (www.editage.jp) for English language editing. This work was supported by JSPS KAKENHI Grant Number 20H03577.

*The author declares no conflict of interest.*

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